JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2025;21(4):315-324 / https://doi.org/10.3988/jcn.2024.0526

Diverse Clinical Phenotypes of Neuronal Intranuclear Inclusion Disease in South Korea

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Background and Purpose Neuronal intranuclear inclusion disease (NIID) is a progressive neurodegenerative disease characterized by a wide range of clinical manifestations. GGC-repeat expansion in *NOTCH2NLC* was recently identified as the genetic cause of NIID. Here we report clinical, radiological, pathological, and genetic findings in NIID patients.

Methods Twenty-five NIID patients from 22 unrelated families of Korean ancestry were reviewed from 9 referral centers in South Korea. We compared clinical features between sporadic and familial NIID patients. We classified NIID patients according to their prominent symptoms. The presence of GGC repeat expansion was analyzed in 19 patients.

Results The 25 reviewed NIID patients comprised 12 (48.0%) sporadic and 13 (52.0%) familial cases, with the latter showing a significantly higher proportion of males (p=0.027). The patients were classified into three subtypes based on the prominent symptoms: NIID-Episodic (44.0%), NIID-EPS (extrapyramidal symptoms) (36.0%), and NIID-Dementia (20.0%). Most patients (92.0%) also exhibited other symptoms, including peripheral neuropathy (60.0%), bladder dysfunction (48.0%), or ophthalmic problems (56.0%). Hyperintensities along the corticomedullary junctions in diffusion-weighted imaging and extensive white-matter hyperintensities in fluid-attenuated inversion-recovery imaging were observed in 96.0% and 100% of the patients, respectively. GGC repeat expansion in *NOTCH2NLC* was identified in 6 sporadic and 10 familial cases. The number of GGC repeats was not correlated with the onset age or clinical symptoms.

Received November 29, 2024
Revised April 3, 2025
Accepted April 8, 2025

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Conclusions This study has highlighted the diverse phenotypes and genetic profiles of Korean NIID patients, and provided valuable insights into this rare disorder.

Keywords neuronal intranuclear inclusion disease; GGC repeat expansion in *NOTCH2NLC*; histopathological findings; Korea cohort; clinical phenotype.

INTRODUCTION

Neuronal intranuclear inclusion disease (NIID, OMIM #603472) is a chronic progressive neurodegenerative disease characterized by eosinophilic intranuclear inclusions in the central and peripheral nervous systems as well as in the internal organs.[1] NIID is characterized by a wide range of onset ages and clinical manifestations, such as pyramidal and extrapyramidal symptoms (EPS), dementia, convulsions, cerebellar ataxia, peripheral neuropathy, and autonomic dysfunction.[1,2] The heterogeneous nature of the disease makes NIID difficult to diagnose. However, advancements in diagnostic methods have facilitated its detection,[1,3] particularly through skin biopsies, which show neuronal inclusions that are both morphologically and immunohistochemically identical to brain autopsy findings.[4,5] Additionally, NIID has characteristic findings in brain magnetic resonance imaging (MRI) such as symmetric hyperintensities in the corticomedullary junction in diffusion-weighted imaging (DWI) and leukoencephalopathy in fluid-attenuated inversion-recovery (FLAIR) imaging.[5,6] More importantly, GGC repeat expansion in the 5'-untranslated region of *NOTCH2NLC* was identified as the genetic cause of NIID,[7-10] leading to the recognition of NIID in various neurodegenerative diseases.[3,11] GGC repeat expansion has been identified in patients with Parkinson's disease (1.1%–1.5%),[10,12,13] essential tremor (0.0%–13.7%),[14-16] Alzheimer's disease (0.4%–1.4%),[10,17] frontotemporal dementia (1.8%),[17] amyotrophic lateral sclerosis (0.0%–0.7%),[18,19] cerebral small-vessel disease (1.11%),[20] Charcot-Marie-Tooth disease (10.6%),[21] and adult-onset leukoencephalopathy (0.0%–19.9%).[22-24]

Despite several reports on the characteristics of NIID in Asian countries,[7,8,25] there is still much to learn about this condition. Although a few case reports[26-28] and a *NOTCH2NLC* screening study of leukoencephalopathies[24] have been reported on for South Korea, a comprehensive investigation of the clinicopathological features and genetic information of the Korean NIID patients has not been reported previously. Here we report clinical, radiological, pathological, and genetic findings in Korean NIID patients.

METHODS

Twenty-eight patients with suspected NIID from 25 unrelated families of Korean ancestry were reviewed from 9 centers: Samsung Medical Center (*n*=17), Haeundae Paik Hospital (*n*=2), Pusan National University Yangsan Hospital (*n*=2), Pusan National University Hospital (*n*=1), Ewha Seoul Hospital (*n*=2), Ewha Mokdong Hospital (*n*=1), Gyeongsang National University Changwon Hospital (*n*=1), Chungnam National University Hospital (*n*=1), and Eulji University Hospital (*n*=1). We modified the diagnostic criteria proposed by Sone et al.[1] to define "probable NIID" when a patient showed clinical, radiological, and pathological features of NIID. Radiological features of NIID indicate white-matter hyperintensities in the corticomedullary junctions in brain MRI, and pathological features in skin biopsies of NIID patients indicate neuronal intranuclear inclusions. We also defined "probable NIID" when a patient showed clinical and radiological features of NIID and had a family member with probable NIID. We defined "definite NIID" when 1) a probable NIID patient also had GGC repeat expansion in *NOTCH2NLC*; or 2) a patient with clinical and radiological features of NIID, who did not undergo a pathological examination, was found to have GGC repeat expansion in *NOTCH2NLC*. A familial NIID case was defined when 1) at least one of the second-degree relatives of a probable NIID patient showed either radiological features of NIID or pathological features of NIID; or 2) at least one of the second-degree relatives of a definite NIID patient showed the same clinical features.[1] Those who were not consistent with the definition of familial NIID were classified as sporadic cases. The diagnosis was confirmed by consensus involving at least two neurologists. The cognitive function of all participants was assessed using the Korean version of the Mini-Mental State Examination (MMSE).[29]

A skin punch biopsy was performed 10 cm above the lateral malleolus or in the abdomen.[4] Obtained tissue samples were fixed in 10% formalin, followed by hematoxylin and eosin staining and immunohistochemical analysis using an antiubiquitin antibody. For electron microscopy observations, the samples were fixed using glutaraldehyde in cacodylate buffer and embedded in epoxy resin.

Genomic DNA was extracted from the peripheral blood of 19 patients and sent to the Department of Human Genetics, Yokohama City University, Japan. Repeat-primed and fluorescence amplicon length polymerase chain reactions were performed to evaluate the presence of pathogenic GGC repeat expansion in *NOTCH2NLC* (Supplementary Material in the online-only Data Supplement). Genetic testing was not performed on 9 of the 28 patients with suspected NIID due to test refusal or death. The genetic analyses were approved by the Institutional Review Board of Samsung Medical Center (2021-05-087), and the participants provided written informed consents. All methods were performed in accordance with the relevant guidelines and regulations.

Three of the 28 patients were excluded after testing negative for GGC repeat expansion in *NOTCH2NLC*, despite having inclusion bodies in skin biopsies and corticomedullary-junction hyperintensities in MRI. To further clarify the genetic background of these three excluded cases, we tested for CGG repeat expansion in *FMR1*. One patient, a 59-year-old male, had an *FMR1* premutation (with 102 CGG repeats) and family histories of dementia (mother) and Landau−Kleffner syndrome (grandson). The other two patients tested negative for CGG repeat expansion in *FMR1*, had no notable family history, and exhibited hyperintensities in FLAIR imaging without diffusion restriction in DWI. Consequently, 25 patients were included in the final analyses: 16 definite and 9 probable NIID cases.

For statistical analyses we applied logistic regression to categorical data and ranked analysis of covariance to numerical data while adjusting for the sex variable to assess differences between sporadic and familial cases. The sex variable itself was analyzed using Fisher's exact test to evaluate differences between the groups. Additionally, the associations between the number of GGC repeats and clinical findings were analyzed in nonparametrically using the Spearman test for correlations and the Kruskal−Wallis test for comparisons across multiple groups, with adjustments for sex.

RESULTS

The clinical, radiological, and genetic features of the 25 patients with probable or definite NIID are presented in Table 1. The median onset age was 62.0 years (interquartile range [IQR]=52.0−65.0 years). Patients were classified into three subtypes according to their most-prominent symptoms: 1) 44.0% of the patients showed recurrent encephalitic episodes such as altered consciousness, confusion, or migraine (NIID-Episodic); 2) 36.0% showed EPS such as gait disturbance, tremor, or ataxia (NIID-EPS); and 3) 20.0% showed a progressive cognitive decline (NIID-Dementia). However, the presenting symptoms overlapped between the subtypes, and 72.0% of the patients developed additional symptoms during the disease course. Overall, the most common symptoms were EPS (72.0%), followed by progressive cognitive decline (64.0%) and recurrent encephalitic episodes (60.0%) (Table 1). Most of the patients with NIID (92.0%) also had other symptoms, such as peripheral neuropathy (60.0%), bladder dysfunction (48.0%), or ophthalmic problems (56.0%) that included cataracts, macular degeneration, and retinitis pigmentosa (Table 1; more details are provided in Supplementary Table 1 in the online-only Data Supplement, and initial symptoms are provided in Supplementary Table 2 in the online-only Data Supplement). The features of definite NIID patients with genetic findings are also summarized in Supplementary Table 3 (in the online-only Data Supplement).

The 25 probable or definite NIID patients comprised 12 sporadic and 13 familial cases (Supplementary Fig. 1 in the online-only Data Supplement). We identified that 6 of the 12 sporadic cases (50.0%) and 10 of the 13 familial cases (76.9%) had pathogenic GGC repeat expansion in *NOTCH2NLC*, with a median of 113.0 repeats (IQR=104.8−126.5 repeats) (Fig. 1). The proportion of males was higher in the familial cases than in the sporadic cases (Fisher's exact test: p=0.027), with 9 of the 13 familial cases (69.2%) being male. There was no difference in onset age, brain MRI findings, MMSE scores, or number of GGC repeats between the familial and sporadic cases after adjusting for sex (Table 1). The number of GGC repeats was not correlated with the symptom onset age (Spearman correlation test: p=0.774) or the subtype (Kruskal−Wallis test: p=0.880) after adjusting for sex.

All patients showed white-matter hyperintensities in the frontal corticomedullary junctions, with varying degrees of extension in FLAIR imaging (Fig. 2). Almost all patients (96.0%) showed symmetric hyperintensities along the corticomedullary junctions in DWI. Longitudinal MRI images from patients who underwent follow-up scans are presented in Supplementary Fig. 2 (in the online-only Data Supplement), which illustrates changes over time. The hyperintensities in DWI and FLAIR imaging gradually increased over time in most patients, whereas in two patients (S7 and F12) the DWI hyperintensities in the corticomedullary junction diminished over time. In Case S7, DWI hyperintensities in the corticomedullary junction of bilateral frontal areas that were observed in July 2018 (arrowhead in Supplementary Fig. 2A in the online-only Data Supplement), had diminished in follow-up DWI. In Case F12, no restriction lesion was observed in DWI in January 2017, but a DWI hyperintensity appeared in the corticomedullary junction of the bilateral frontal areas in April 2022 (arrowhead in Supplementary Fig. 2B in the online-only Data Supplement), which had subsequently decreased in intensity by February 2023. These

Table 1. Clinical, radiological, and genetic features of the patients with probable or definite NIID

Variable	Total (*n*=25)	Sporadic cases				Familial cases				p^*
		Total (*n*=12)	Subtypes			Total (*n*=13)	Subtypes			
			NIID-Episodic (*n*=4)	NIID-EPS (*n*=5)	NIID-Dementia (*n*=3)		NIID-Episodic (*n*=7)	NIID-EPS (*n*=4)	NIID-Dementia (*n*=2)	
Onset age (yr)	62.0 [52.0–65.0]	62.5 [60.0–64.5]	60.0 [53.5–64.8]	63.0 [61.0–64.0]	62.0 [62.0–66.0]	55.0 [51.0–65.0]	59.0 [46.8–65.3]	65.0 [60.0–66.0]	50, 51	0.414
Disease duration (yr)	4.0 [2.5–9.5]	4.0 [3.0–9.0]	7.0 [3.25–10.0]	3.0 [1.0–7.0]	4.0 [3.0–6.0]	5.0 [2.0–9.5]	4.0 [2.0–9.0]	3.5 [0.5–8.0]	10, 18	0.796
Sex, male:female	12:13	3:9	1:3	2:3	0:3	9:4	6:1	3:1	0:2	0.027
Clinical phenotypes										
Progressive cognitive decline	16 (64.0)	6 (50.0)	3 (75.0)	0 (0)	3 (100)	10 (76.9)	6 (85.7)	2 (50.0)	2 (100)	0.226
Encephalitic episode	15 (60.0)	6 (50.0)	4 (100)	1 (20.0)	1 (33.3)	9 (69.2)	7 (100)	1 (25.0)	1 (50.0)	0.428
EPS	18 (72.0)	9 (75.0)	1 (25.0)	5 (100)	3 (100)	9 (69.2)	3 (42.9)	4 (100)	2 (100)	>0.999
Other symptoms										
Peripheral neuropathy	15 (60.0)	7 (58.3)	2 (50.0)	3 (60.0)	2 (66.7)	8 (61.5)	3 (42.9)	3 (75.0)	2 (100)	>0.999
Bladder dysfunction	12 (48.0)	6 (50.0)	1 (25.0)	2 (40.0)	3 (100)	6 (46.2)	3 (42.9)	2 (50.0)	1 (50.0)	0.848
Ophthalmic problems	14 (56.0)	5 (41.7)	2 (50.0)	2 (40.0)	1 (33.3)	9 (69.2)	5 (71.4)	2 (50.0)	2 (100)	0.165
MRI										
Hyperintensities in DWI	24 (96.0)	11 (91.7)	4 (100)	4 (80.0)	3 (100)	13 (100)	7 (100)	4 (100)	2 (100)	0.480
Hyperintensities in FLAIR imaging	25 (100)	12 (100)	4 (100)	5 (100)	3 (100)	13 (100)	7 (100)	4 (100)	2 (100)	>0.999
MMSE score	26.0 [21.0–28.0]	25.0 [21.0–27.0]	23.5 [19.3–23.5]	27.0 [26.0–29.0]	24.0 [23.0–25.5]	26.0 [20.5–28.0]	28.0 [20.0–28.5]	26.0 [25.5–27.5]	16, 25	0.891
GGC repeat expansion in *NOTCH2NLC*	16/19	6/9	1/2	3/3	2/4	10/10	6/6	2/2	2/2	
Number of GGC repeats	113.0 [104.8–126.5]	108.5 [95.8–120.0]	116	107.0 [89.0–108.5]	104, 132	116.0 [108.3–126.5]	109.5 [99.5–113.5]	127, 130	118, 125	0.356

Data are median [interquartile range], *n* (%), *n*:*n*, or *n*/*n* values. For subgroups with small sample sizes (*n*=1 or 2), individual values are presented in place of median values.
*Comparisons between sporadic and familial cases after adjusting for sex. *p* values were calculated using the chi-square test for categorical data and ranked analysis of covariance for numerical data.
DWI, diffusion-weighted imaging; EPS, extrapyramidal symptoms; FLAIR, fluid-attenuated inversion-recovery; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NIID, neuronal intranuclear inclusion disease.

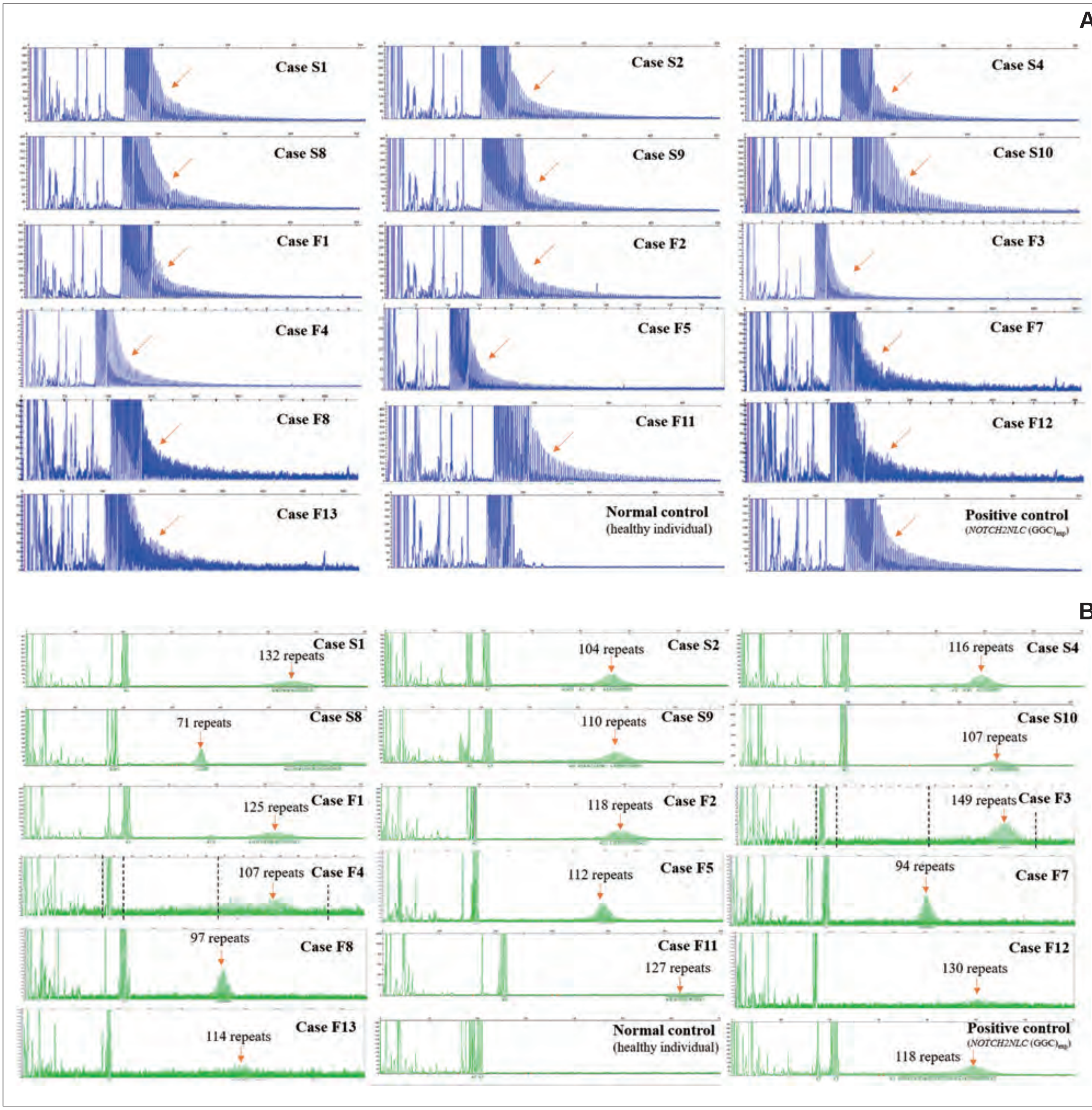

Fig. 1. Results from the repeat-primed polymerase chain reaction (A) and the amplicon length polymerase chain reaction (B).

observations are consistent with previous studies suggesting that DWI lesions are not always present in NIID.[30-32] It was particularly interesting that in the hyperintensity observed in the cortical area of the right parieto-occipital lobe in DWI in Case F4 (arrow in Supplementary Fig. 2B in the online-only Data Supplement) appeared to be associated with acute-onset hemianopsia, which had disappeared 1 year later in follow-up imaging as the symptoms improved.

Nineteen patients underwent skin biopsies, all of whom showed neuronal intranuclear inclusions, indicating probable NIID (Fig. 3). Inclusion bodies were found in fibroblasts, sweat gland cells, and adipocytes (Supplementary Table 4 in the online-only Data Supplement).

DISCUSSION

Here we have reported the diverse phenotypes of Korean NIID patients. We have presented clinical and radiological findings from 25 probable or definite NIID patients, pathological findings from 19 probable or definite NIID patients, and genetic findings from 16 definite NIID patients, thereby providing a comprehensive overview of the heterogeneous

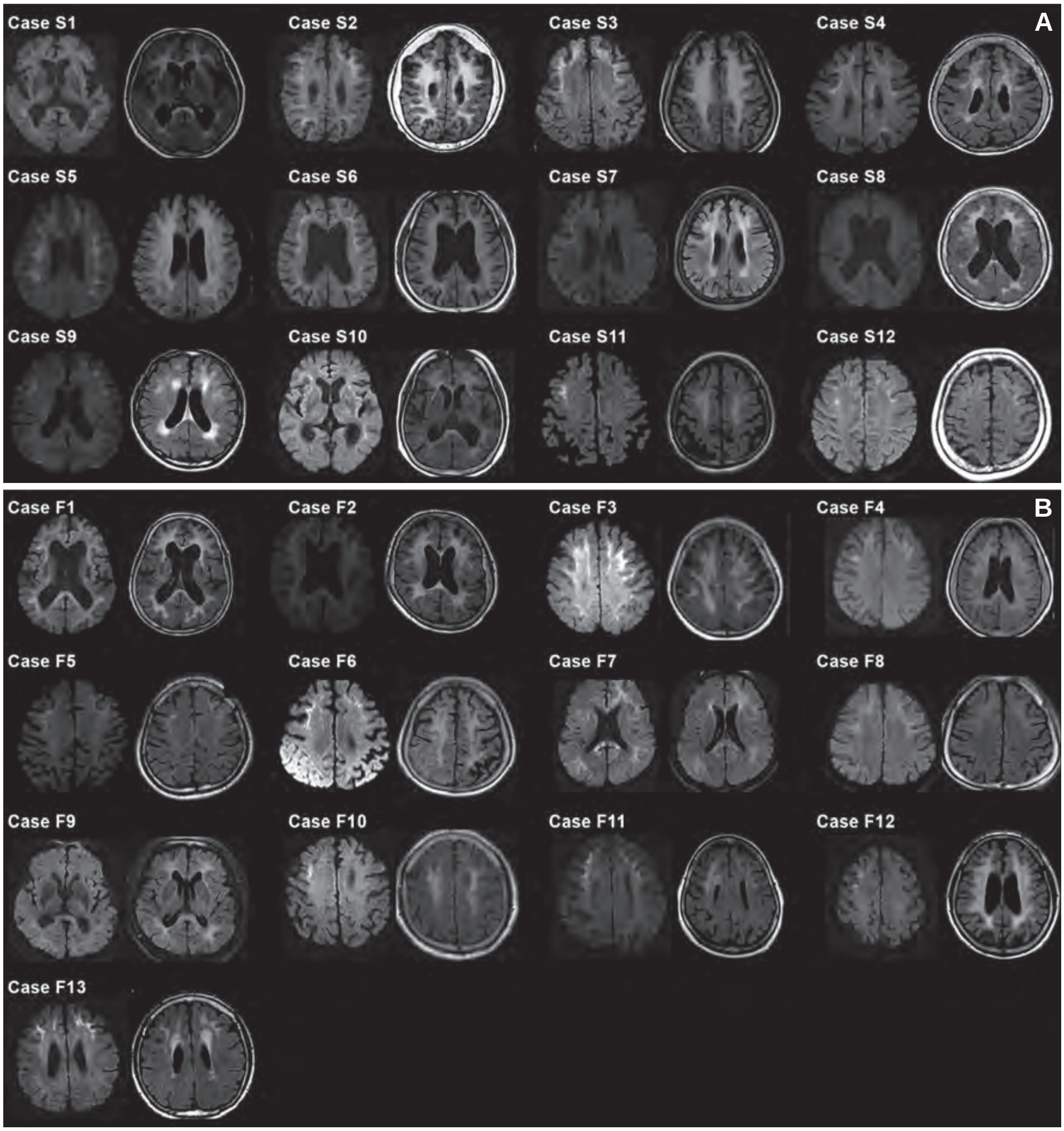

Fig. 2. Brain imaging findings of the sporadic (A) and familial (B) NIID patients (left, DWI; right, FLAIR imaging). DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion-recovery; NIID, neuronal intranuclear inclusion disease.

presentation of Korean NIID patients.

Korean NIID patients showed diverse clinical symptoms. According to the prominent symptoms, NIID-Episodic (44.0%) was the most common subtype, followed by NIID-EPS (36.0%) and NIID-Dementia (20.0%). However, as the disease progressed, most patients (72.0%) developed multiple additional symptoms, including EPS (72.0%), progressive cognitive decline (64.0%), or recurrent encephalitic episodes (60.0%). NIID patients have been reported to exhibit dementia (40.0%–93.3%), EPS (22.5%–44.4%), encephalitic episodes (5.0%–66.7%), and muscle weakness (33.3%–53.3%).[1,3,8,15,33] The subtypes of previously reported cases from South Korea were NIID-Episodic (53-year-old female,[27] 56-year-old female, and 54-year-old male[28]) and NIID-Dementia (65-year-old female).[26] Several classifications of NIID have been proposed due to the heterogeneity of this condition. A study conducted in Japan by Sone et al.[1] suggested classification into dementia-dominant and limb-weakness-dominant subtypes. A study conducted in China by Sun et al.[15] suggested classification into muscle-weakness-dominant, dementia-dominant, and parkinsonism-dominant subtypes. Additionally, it has been suggested that NIID can be classified into four subgroups based on the initial or main manifestations: dementia-dominant, movement-disorder-dominant, muscle-weakness-

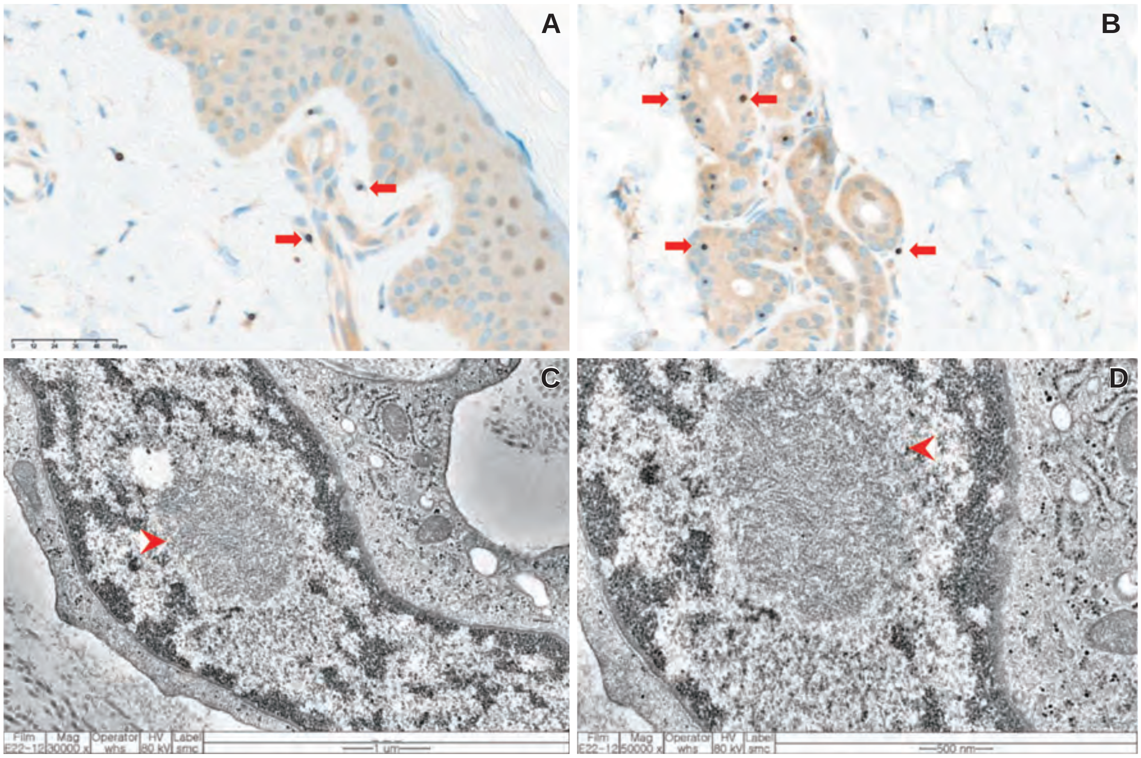

Fig. 3. Histological findings of a skin biopsy of a representative case (S8). A and B: Ubiquitin-positive intranuclear inclusions were identified in the fibroblasts and sweat gland epithelial glands (arrows). Sections were fixed in 10% formalin and stained with hematoxylin and anti-ubiquitin antibody (magnification: A, ×400; B, ×400). C and D: Ill-defined filamentous inclusions were evident in the nuclei of fibroblasts (arrowheads). The inclusions were not bound by a membrane, and they ranged in size from 0.6 μm×0.6 μm to 1.7 μm×0.9 μm (C: ×30,000; D: ×50,000).

dominant, and paroxysmal-symptom-dominant subtypes (also from a study conducted in China).[10,34] In contrast to the classifications suggested by Sone et al.[1] and Sun et al.,[15] our proposed NIID-Episodic subtype distinguishes patients who primarily present with recurrent encephalitic episodes, who accounted for 44.0% of the present cases. This subtype represents a distinct group of patients who do not fit into existing dementia-dominant or movement-disorder-dominant categories, but closely resemble the previously described paroxysmal-symptom-dominant subtype,[10,34] suggesting a phenotypic variation. Additionally, our cohort contained a high proportion of patients with EPS or dementia, but no limb-weakness-dominant case. This may reflect the characteristics of NIID in patients of Korean ancestry, or it may have been influenced by the lack of young patients in our cohort, given that limb weakness occurs mainly in patients aged 30–40 years.[1] However, given the smallness of the sample, further studies are needed to validate this observation. The diverse clinical spectrum reflects the heterogeneous nature of NIID and underscores the need to conduct studies with a larger numbers of patients to reach a classification consensus.

Furthermore, most of our NIID patients (92.0%) experienced other symptoms or signs. Peripheral neuropathy was present in 60.0% of the patients, including 11 asymptomatic patients, while 48.0% had bladder dysfunction and 56.0% had ophthalmic problems. The proportion of patients with other symptoms was largely consistent with previous studies in Japan and China,[1,8,35-37] confirming that patients with NIID should be evaluated for these symptoms.

Our NIID cohort comprised 48.0% sporadic and 52.0% familial cases, with the proportion of males being higher in the familial cases. Sone et al.[1] found a higher prevalence of females than males in both sporadic and familial cases. However, another study found that females were more prevalent in sporadic cases and that males were more prevalent in familial cases,[10] which aligns with our findings. Further extensive investigations are therefore necessary to fully characterize the sex distribution in NIID.

Our radiological investigations showed that all patients had white-matter hyperintensities in the corticomedullary junctions, with varying degrees of extension in FLAIR imaging. However, DWI hyperintensities were not found in one patient. This was consistent with other East Asian studies[34,38] finding that while most NIID patients exhibited DWI hyperintensities along the corticomedullary junctions, it was not present in all cases. Longitudinal MRI findings revealed that hyperintensities in DWI and FLAIR imaging gradually increased over time in all except two patients (S7 and F12).

Indeed, previous case reports either initially found DWI hyperintensities that subsequently disappeared[30] or found hyperintensities to be initially absent before being subsequently observed.[31] Cytotoxic edema withdrawal, subsequent neuronal loss, and gliosis might account for the disappearance of DWI hyperintensities.[30]

Pathological investigations of the skin biopsy samples frequently detected inclusion bodies in fibroblasts and sweat gland cells. This finding is consistent with a previous report of a high frequency of inclusion bodies within sweat gland cells.[39]

The genetic findings showed that the number of GGC repeats in *NOTCH2NLC* was not associated with the onset age or subtypes based on prominent symptoms. A previous study suggested that the number of repeats was not associated with the onset age,[10] while another study indicated that a larger number of repeats was correlated with an earlier onset age.[34] Consistent with our findings, a previous study found no significant differences in the number of repeats across different clinical phenotypes,[33] whereas another study found that there were more repeats in the muscle-weakness subtype.[34] A recent study from South Korea found that there were fewer GGC repeats in patients presenting with encephalitic-like episodes.[24] Previous studies have found that the presence of >200 GGC repeats was associated with muscle weakness, 100 to 200 GGC repeats led to a dementia phenotype,[10,40] and <100 GGC repeats were associated with a parkinsonism phenotype.[12] Establishing an association between the number of repeats and onset age in NIID can be challenging. The smallness of our sample may explain why we did not find a significant correlation between the number of GGC repeats and clinical symptoms. Further studies with a larger samples of Korean NIID patients are necessary to accurately characterize any such association. Furthermore, recent studies of animal models and human neural progenitor cell models suggest that GGC repeat expansions in *NOTCH2NLC* contribute to NIID pathology via multiple mechanisms, including polyglycine protein aggregation and the formation of intranuclear inclusions,[41] mitochondrial dysfunction,[42] microglial activation,[43] and ribonucleic acid toxicity,[44] ultimately leading to neurodegeneration and associated clinical features.[35,45] Integrating molecular mechanisms with clinical manifestations in future studies may help to refine the phenotype−genotype correlations in NIID.

While NIID is considered an autosomal dominant disorder, its penetrance varies among affected families. Recent studies suggest that the number of GGC repeats alone does not fully determine disease onset, since expansions exceeding 200−300 repeats can trigger the hypermethylation of adjacent CpG islands. This leads to transcriptional downregulation and the carriers being free from symptoms.[44,46] Notably, large numbers of hypermethylated, nonpathogenic GGC repeats in asymptomatic male carriers have been reported to contract to pathogenic numbers of repeats during spermatogenesis, contributing to somatic mosaicism and a paternal bias in NIID transmission.[47] Moreover, variations in copy number of *NOTCH2NLC* and the potential compensatory effects of *NOTCH2NLA* and *NOTCH2NLB* suggest additional complexity in inheritance patterns.[35] Given the observed instability in the number of repeats, epigenetic modifications, and possible genetic modifiers, further research integrating long-read sequencing and epigenetic profiling is essential to better understand the inheritance mechanisms of NIID.

While there is no curative treatment for NIID, anti-inflammatory drugs or steroid pulse therapy can be effective in reducing cerebral edema and improving consciousness in the short term for patients with the NIID-Episodic subtype.[1,11] Indeed, steroid treatment resulted in 4 of 11 patients with the NIID-Episodic subtype experiencing improvement in headache or confusion within 1 week. However, it remains unclear whether these improvements were due to the natural course of the disease or the effect of the steroids. Early diagnosis may guide the prompt use of anti-inflammatory drugs or steroids in episodic events.

This study had several limitations. First, the sample was relatively small and nine of the probable NIID patients did not to undergo genetic testing for *NOTCH2NLC*. The smallness of the sample may have been responsible for us not identifying significant differences between sporadic and familial cases, or correlations between the number of GGC repeats and clinical features. Second, we did not perform comprehensive screening for other genes associated with neuronal intranuclear inclusions.[48] However, CGG repeat expansion in *FMR1* was tested in four of nine probable NIID patients. All four probable NIID patients were negative, supporting the diagnosis of NIID and minimizing misclassification. This finding highlights the importance of differential genetic testing in suspected NIID cases, particularly for disorders with overlapping clinical and radiological features, such as fragile X-associated tremor/ataxia syndrome. Third, selection bias might have been present since our patients were primarily recruited from neurodegeneration clinics, leading to an older cohort with a higher prevalence of cognitive and neurodegenerative symptoms, and an absence of muscle-weakness cases. Future studies should recruit larger samples from wider ranges of clinical settings and age groups in order to better understand the diverse phenotypes associated with NIID. Fourth, not all family members of the patients were available for performing skin biopsies or genetic tests. Nevertheless, our study is valuable since we extensively showed the diverse phenotypes of NIID patients of Korean ancestry.

In conclusion, we have comprehensively analyzed the clinical, radiological, pathological, and genetic characteristics of NIID in Korean patients, with the findings representing important contributions to the understanding of NIID. Detailed insights into the pathological and genetic landscape of NIID can lead to the development of more-effective diagnostic and therapeutic strategies in clinical practice.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2024.0526.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to patient privacy and ethical restrictions, but are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (RS-2022-NR070487); ICT Creative Consilience Program through the Institute of Information & Communications Technology Planning & Evaluation (IITP) grant funded by the Korea government (MSIT) (RS-2020-II201821); Future Medicine 2030 Project of the Samsung Medical Center [#SMX1250081]; a faculty research grant of Yonsei University College of Medicine (6-2023-0145); the Japan Agency for Medical Research and Development (AMED) (JP24ek0109674, JP24ek0109760, JP24ek0109617, JP24ek0109648, and JP24ek0109677); the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant-in-Aid for Scientific Research (C) (JP23K27568 and JP24K02230), and the Takeda Science Foundation.

Acknowledgements

We sincerely thank the patients for their participation in this study. We would also like to express our special gratitude to Mr. Yong-Sun Cho, Mrs. Myeong-Deok Jo, and Mr. Se-Jeong Im for their contribution to the Medical Research Fund at Samsung Medical Center.

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